

A Study on Olfactory Dysfunction in Various subtypes of Parkinsonism

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CERTIFICATE

This is to certify that this dissertation entitled “**A study on Olfactory Dysfunction in various subtypes of Parkinsonism**” submitted by **Dr. M.JAWAHAR** appearing for **D.M.,Branch-I Neurology** Degree examination in August 2008 is a bonafide record of work done by him under my direct guidance and supervision in partial fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India.

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DECLARATION

I solemnly declare that the dissertation titled "**A study on Olfactory dysfunction in various subtypes of Parkinsonism**" is done by me at Institute Of Neurology, Madras Medical College & Govt. General Hospital, Chennai, during 2005-2008 under the guidance& supervision of **Prof. Geetha Lakshmipathy, M.D.D.M.**

The dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University towards the partial fulfillment of requirements for the award of D.M. Degree in Neurology.

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INTRODUCTION

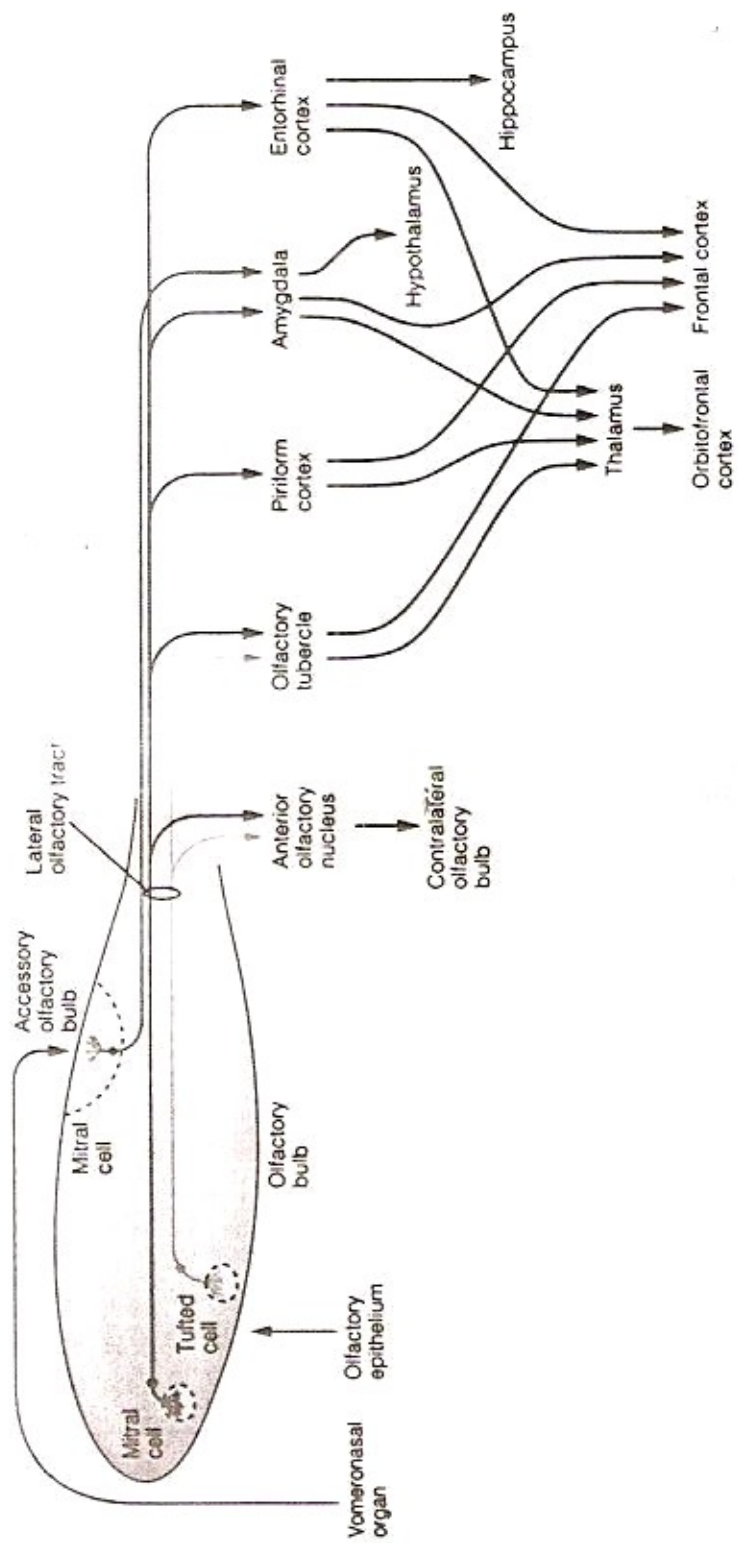
Impairment of olfaction in Parkinson's disease (PD) was first recognized in the 1970s^{1,2}, but it is mainly in the past decade that insights into its pathogenic basis and specificity have occurred. Various degrees of olfactory dysfunction occur in some other Parkinsonian syndromes, but a marked reduction in the sense of smell remains a highly characteristic feature of PD. The early or pre clinical detection of Parkinson's disease is increasingly recognized as an area in which olfactory testing may be of value. Research findings have confirmed a role for olfactory testing in the differential diagnosis of movement disorders, and suggest that this approach is currently underused in clinical practice. Validated test batteries are now available that may prove to be of practical use in the differential diagnosis of Parkinsonian syndromes and indeterminate tremors.

REVIEW OF LITERATURE

HISTORY

Since the pioneering work of Valentin (1848), who determined the lowest concentration of an odorous gas that a subject could perceive, a plethora of nominally distinct olfactory tests has been developed, including tests of sensitivity (e.g., odor detection and recognition thresholds), discrimination, identification, memory and suprathreshold intensity (for reviews, see Cain, 1978; Doty, 1991, 1992; Engen, 1982; Koster, 1975; Takagi, 1989; Wenzel, 1948). Katerina Markopoulou et al, Doty et al & Stern et al have extensively studied olfactory functions in various types of parkinsonian patients and they have found out the usefulness of doing olfactory function tests in the diagnosis of various subtypes of parkinsonism. Doty et al have developed the olfactory function test kit, the University of Pennsylvania Smell Identification Test (UPSIT) in 1988 and have researched in detail about the olfactory impairment in various neurodegenerative diseases like parkinsonism, various types of dementia and hereditary ataxias.

Anatomy of the olfactory tract is illustrated in the next page.



OLFACTORY SYSTEM STRUCTURE AND ORGANIZATION

The olfactory system is composed of the olfactory epithelium, the olfactory nerves, the olfactory bulbs, the olfactory tracts, and the median and lateral olfactory striae that terminate in the contralateral hemisphere or the ipsilateral amygdaloid nucleus, septal nuclei and hypothalamus. The olfactory epithelium is located on the superior- posterior aspect of the nasal septum and lateral walls of the nasal cavity and contains the olfactory sensory neurons (OSNs). The OSNs are generated in situ from stem cells. Aging OSNs are replaced by cell division that persists into adulthood and throughout the adult life. The life span of an OSN is in the range of weeks to months. The OSNs are bipolar neurons, the axons of which form the olfactory nerves and pass through the cribriform plate and terminate in the olfactory bulb, where they synapse with second order neurons and interneurons. In the olfactory bulb, the OSN axon terminates in a glomerulus differs in different mammalian species. The axon of the second-order neurons form the olfactory tracts located in the orbit surfaces of the frontal lobes.

As it courses centrally, the olfactory tract becomes divided into the median and lateral olfactory striae. In an organization analogous to that of the visual pathways, median stria fibres decussate through the anterior commissure, join fibres from the opposite olfactory tract, and terminate in the contralateral hemisphere, while lateral striae fibers

reach the primary olfactory cortex (piriform cortex) and terminate in the ipsilateral amygdaloid nucleus, septal nuclei, and hypothalamus.

In humans, odor detection of airborne odorants appears to be very efficient, but odor discrimination is considerably less efficient. Olfactory perception is initiated by the activation of odorant receptors by odorous ligands. Airborne odorants stimulate the olfactory sensory neurons (OSNs), contained in the olfactory epithelium. It is thought that the functional heterogeneity of the OSNs is derived from a very large number of odorant receptors (OR) that are expressed in the OSNs. In the last decade, approximately 1000 odorant receptors (OR) genes have been identified in humans. These represent approximately 1% of the human genome. Interestingly, a large subset (almost two-thirds) of these genes appears to be nonfunctional; ie., they are pseudogenes. The OR genes are distributed in clusters on all chromosomes except chromosome 20 and the Y chromosome. This clustering has been observed in many different species, including mice, rats, zebrafish and humans. There does not appear to be any particular pattern to be clustering of the OR genes, and they can often be intermixed with other gene families such as T-cell receptor and beta-globin genes. The OR genes are intronless and have open reading frames (ORF) of approximately 1kb. Based on amino acid similarity they have been categorized into families and subfamilies. The predicted amino acid sequence indicates the presence of seven transmembrane domains, a characteristic of G-protein coupled receptors. Each OSN expresses a single allele of a single OR gene² and

therefore the olfactory epithelium consists of distinct OSN populations (reviewed in References 82 through 84).

How is the sensitivity of OSN translated into the specificity of individual smell? The principles underlying this specificity are still a matter of debate, but some interesting patterns are emerging. Both peripheral and central mechanisms seem to play an important role. In the periphery, specificity appears to be generated both by the OSN expressing a single allele of a single OR gene and by the pattern of connections that the OSN forms. All neurons expressing a single OR gene project axons that synapse in one medial and one lateral glomerulus of the olfactory bulb, which represents the first relay station of the olfactory pathway. It appears that the OR plays a role of organizing the connectivity of the olfactory map³. The glomerulus containing the second order neurons appear to serve as an “odorant feature” via mechanisms involving lateral feedback inhibition and excitation and temporal synchrony. Interestingly, in rodents, voltage sensitive dye imaging has revealed that there are differences in the response latency and the response time course across different glomeruli in the olfactory bulb. The pattern of activity at the level of glomerulus evolves over time and depends also on the identity of the different glomeruli. Both the temporal and the spatial context of the odor-evoked response is critical. The temporal patterning may be imposed both by the odor carrier medium, the sampling activity, or by the inherent neural dynamics of the cells comprising the olfactory bulb^{4,5}. At the system level, it has been proposed that all odors

are initially encoded as “objects” in the piriform cortex and that odor perception depends on higher cognitive functions such as memory and neural plasticity⁶.

Odors have long been thought to be linked to emotional responses, yet an association at the anatomical level has only recently been clearly demonstrated. Studies of patients with focal brain injuries suggest that the caudal orbitofrontal and medial temporal cortices are involved in odor perception. Using event-related fMRI⁷, researchers were able to show the responses could be identified in the piriform cortex in a rostrocaudal axis. The amygdala was activated bilaterally by all odors, regardless of valence. In the posterior orbitofrontal cortex, pleasant odors segregated in the lateral aspects. fMRI studies have shown that odors can activate the cerebellum in a concentration-dependent manner⁸. These studies provide direct evidence in humans of the heterogeneity of brain regions involved in odor processing and that there is coupling between olfaction, emotion, and higher cognitive processes. At the same time, this heterogeneity of brain regions involved in normal nervous system function indicates its vulnerability in disease states and neurodegenerative processes.

In summary, the analysis of the olfactory system at the molecular, cellular, and system level has identified a rather complicated organization that implicates both

peripheral and central components in the function of the olfactory system. The characterization of the olfactory deficit in neurodegenerative disorders—specifically in Parkinson's disease and parkinsonian syndromes—has the potential to provide significant insights into its function in the normal and disease states, it should provide insight into the interplay of different aspects of central nervous system function in neurodegeneration.

ASSESSMENT OF OLFACTORY FUNCTION

In humans, different methods have been developed to assess distinct aspects of olfactory function, such as odor identification, threshold detection, and odor recognition memory. A number of these methods have achieved widespread use of both in the research and clinical domain.

A commonly used test is the University of Pennsylvania Smell Identification Test (UPSIT), developed by Doty et al^{9,10}. Its widespread use is based on the ease of administration, the relatively short completion time and its high test – retest reliability. This test uses 40 odorants that are released by using a pencil to scratch the surface of a strip containing a microencapsulated odorant. The subject is asked to identify each odorant by choosing among four items in a multiple-choice fashion. A simplified version of UPSIT is the CC-SIT developed by Cain and Rubin¹¹. In the test, odor identification

is combined with threshold testing. Threshold testing is performed using plastic squeeze-bottles containing successive dilutions of n-butanol in water, using 4% n-butanol as the highest concentration. For odor identification, the subjects sniff eight glass bottles containing different odorants and choose in a multiple-choice fashion from a uniform list of 16 items. More recently, Hummel et al. developed a new test using a pen like odor-dispensing device¹². This test assesses odor threshold (by using n-butanol in a stepwise presentation), odor discrimination (16 pairs of odorants and triple-forced choice), and odor identification (by using 16 common odorants and a multiple forced-choice from among four verbally stated options per odorant). Other tests include the San Diego Odor Identification test¹³, the Scandinavian Odor Identification test¹⁴, the Viennese Olfactory Test Battery¹⁵ and Smell Threshold Test¹⁶.

Olfactory event related potentials (OERP) have been recorded in control and affected individuals in response to randomized stimulation with different odorants and the OERP latencies have been determined in control and affected individuals¹⁷. Statistical reliability of the OERP was established by Thesen et al¹⁸, and it was shown that reliability of OERPs is comparable to that of visual and auditory evoked potentials. The generators for the OERP waveforms are not known. The early waveform (PI) is thought to originate in the olfactory bulb and the late waveform (P3) in the olfactory cortex¹⁹.

To determine whether anatomical changes are associated with olfactory dysfunction, endoscopic techniques have been developed to obtain olfactory epithelium from human subjects under either general or topical anesthesia^{21,22}. The tissue is examined by light and / or electron microscopy and histochemistry²³. The usefulness of this procedure is limited, since it is invasive and may require general anesthesia. The olfactory epithelium and the anterior olfactory nucleus can also be obtained postmortem and examined histologically and histochemically²⁴.

In summary, a number of methods are currently available to assess olfactory function in humans. The choice of method depend on the ease of administration and on the aspect of olfactory function that is being assessed.

OLFACTORY DYSFUNCTION IN NORMAL AGING

A number of studies have shown that olfactory dysfunction is affected by aging²⁵⁻²⁷. Olfactory impairment associated with normal aging involves odor identification, threshold detection²⁶, and odor recognition memory²⁸. Olfactory function declines after age 65 and is severely affected after age 80. Interestingly, in women, olfactory impairment appears later in men²⁵.

It is useful to consider olfactory dysfunction contextually in light of finding that the olfactory epithelium undergoes continuous regeneration throughout development and adult life. A number of endogenous and exogenous mechanisms are implicated in maintaining a balance between regeneration and degeneration. Recently, Wu et al²⁹. have shown that signals from neurons within the olfactory epithelium have the ability to inhibit the generation of new neurons by neural progenitors. IN more general terms, it appears that neural repair of the mature CNS may be inhibited by the cellular and molecular microenvironment³⁰. It is not clear what the role of these mechanisms is in aging or neurodegenerative disease. Cumulative exposure to environmental toxins, chemicals, upper respiratory viral infections, or head injury could contribute to gradual olfactory impairment by interfering with endogenous mechanism of regeneration.

OLFACTORY DYSFUNCTION IN PARKINSON'S DISEASE (PD)

Olfactory dysfunction has been clearly demonstrated in sporadic PD. Olfactory dysfunction in this disorder includes impairment in odor identification, threshold detection, and odor recognition memory³¹. It has been shown that olfactory dysfunction is present early in the disease process and appears to remain stable as the disease progresses³². Studies have attempted to correlate olfactory dysfunction disease parameters such as disease stage, duration, subtype, cognitive dysfunction, and therapy. Interestingly, olfactory dysfunction appears to be independent of disease stage and

disease duration³². In contrast, olfactory dysfunction appears to be dependent on disease subtype, suggesting that disease subtype confers the specificity of the olfactory impairment. In a study by Stern et al., olfactory function was assessed in different PD subtypes³³. Olfactory function was more impaired in advanced PD (Hoehn and Yahr stage III or greater) than early PD (Hoehn and Yahr stage II or less for four or more years). Both postural instability-gait disorder (PIGD) predominant PD (defined as UPDRS mean tremor score/ mean PIGD score <1.0) and tremor-predominant PD (defined as UPDRS mean tremor score/mean PIGD score <1.0) and tremor-predominant PD (defined as UPDRS mean tremor score/mean PIGD score >1.5) subtypes exhibited olfactory impairment, but the impairment was more severe in the PIGD form than in the tremor-predominant form of PD. It is conceivable that the differences in the degree of olfactory impairment between the disease subtypes may reflect different pathophysiological processes in the two disease subtypes. The olfactory deficits associated with PD appear to be independent of the cognitive dysfunction associated with the disease³⁴. Olfactory dysfunction in PD is bilateral and does not respond to antiparkinsonian therapy³⁵.

Olfactory impairment in PD has been attributed to the pathological changes, including neuronal loss and the presence of Lowy bodies identified in the olfactory cortex²⁴ and the amygdala³⁶. Interestingly, sniffing impairment appears to contribute to the olfactory impairment in PD⁸.

OLFACTORY DYSFUNCTION IN PARKINSONISM – PLUS SYNDROMES (PPSs)

Olfactory function has also been assessed in multiple system atrophy (MSP), Shy-Drager syndrome³⁷⁻³⁸, progressive supranuclear palsy (PSP)³⁸⁻³⁹ and the parkinsonism-dementia complex of Guam⁴⁰. Wenning et al³⁸ compared olfactory dysfunction in a large series of patients with either PD, MSA, corticobasal degeneration (CBD), or PSP. They showed that impairment of olfactory dysfunction was significantly more pronounced in PD than in PPS. In particular, olfactory impairment was mild in MSA, whereas olfactory function was preserved in CBD and PSP. The findings from A STUDY BY Muller et al (2002) appear to confirm this difference in olfactory impairment between sporadic PD and PPS⁴¹. This consistent difference in olfactory function can therefore be used as an aid in the differential diagnosis of PD and PPS.

Olfactory dysfunction has also been reported in the ALS-parkinsonism-dementia complex of Guam (PDC)⁴². All four forms of the syndrome (ALS, pure parkinsonism, pure dementia, and parkinsonism-dementia complex) show impairment of olfactory function. This suggests a common mechanism of olfactory impairment in the different forms of the syndrome. There are no significant differences in the degree of the olfactory impairment in PD and PDC, making it impossible to distinguish these two entities on the

basis of olfactory impairment⁴⁰.

In contrast to what is seen in the sporadic forms of PPS, olfactory function is impaired in familial forms of PPS. Affected members Of PPS kindreds show impairment similar to that seen in kindreds with idiopathic PD (IPD) phenotypes. Markopoulou et al⁴³ assessed olfactory function in several multigenerational kindreds with an IPD phenotype as well as in kindreds with a PPS phenotype. Olfactory dysfunction appears to be a component of the clinical phenotype in kindreds types of kindreds. No statistically significant differences in the degree of olfactory impairment were observed between these two phenotypes. Thus, it appears that , in regard to olfactory function, sporadic and familial forms of PD and PPS behave differently.

Three different genes are associated with the forms of parkinsonism assessed by Markopoulou et al. One is the alpha-synuclein gene (Family H)⁴³, a second is the gene for the microtubule-associated protein tau (pallido-ponto-nigral degeneration, PPND Family)⁴⁴ and the third is an as-yet unidentified gene on chromosome 2p13⁴⁵. The expression of alpha-synuclein, along with that of its congeners beta-and gama-synuclein, has been assessed in the olfactory mucosa of patients with PD, Lewy body disease, MSA, AD, and healthy controls⁴⁶. While the synucleins are differently expressed in the olfactory epithelium, and alpha-synuclein is the most abundantly expressed protein, there is no significant difference between affected individuals and healthy controls. However,

it is conceivable that alpha- synuclein may play a role in the regeneration of the olfactory epithelium. This hypothesis is supported by other studies in which alpha- synuclein has been implicated in neuronal survival⁴⁷⁻⁴⁸.

To summarize, the presence of olfactory dysfunction in familial forms of parkinsonism associated with a monogenic defect suggests that genetic factors either directly or indirectly underlie olfactory dysfunction.

OLFACTORY DYSFUNCTION IN ATYPICAL PARKINSONIAN SYNDROMES (PPSs)

Olfactory function has been assessed in other atypical parkinsonian syndromes such as MPTP-induced parkinsonism. In this entity, olfactory function is preserved⁴⁹. Olfactory function is also preserved in two syndromes that may be associated with PD, essential tremor⁵⁰⁻⁵¹, and idiopathic restless leg syndrome⁵². While in sporadic forms of these syndromes, they appear to behave as independent disorders: in familial forms of PD, PD and essential tremor phenotypes appear to be associated at the genetic level and possibly reflect differential expressivity of the same monogenic defect⁵³.

OLFACTORY DYSFUNCTION IN OTHER NEURODEGENERATIVE DISEASES

Perhaps not surprisingly, olfactory function is impaired in other neurodegenerative diseases such as Alzheimer's disease (AD)^{15,19,31}, motor neuron disease (MND)⁵⁴⁻⁵⁶, and Huntington's disease (HD)⁵⁷⁻⁶⁰.

In AD, the olfactory impairment appears to occur early in the disease process⁶¹. Interestingly, the ApoE epsilon-4 allele, a known risk factor for AD, appears to correlate with cognitive impairment and odor identification decline^{62,63}. A meta analysis of studies of olfactory function in AD and PD³¹ suggests that olfactory impairment is relatively uniform in these diseases. This is consistent with the phenotypic overlap observed in the clinical manifestations of AD and PD. However, interesting differences exist in the olfactory impairment between AD and PD. In both PD and ad, odor identification is impaired⁶⁴, but AD patients showed a higher olfactory threshold and poorer odor memory performance. In AD, olfactory impairment also appears to be a function of disease duration⁶⁴, whereas this is not the case in PD³². In AD, the olfactory bulb, AON, piriform cortex, amygdale, and hippocampus show neurofibrillary tangles and amyloid plaques⁶⁵⁻⁶⁷. In PD, there is neuronal loss and Lewy bodies (LB) in the AON. The LB, however, resemble more the cortical than the nigral LB²⁴. In addition, there are specific changes in the amygdala of PD patients⁶⁸.

In motor neuron disease, the reports are somewhat conflicting. Some studies report olfactory impairment⁵⁴⁻⁵⁵, while others do not⁵⁶. This could reflect selection bias and heterogeneity in the patient cohorts included in those studies.

In HD, the olfactory deficit is found only in affected individuals and not in genotype-positive asymptomatic individuals⁵⁸. The olfactory deficit involves primarily impairment of olfactory detection and odor identification but not odor recognition memory. As in AD and PD, the olfactory deficit in HD appears early in the disease process⁵⁹⁻⁶⁰.

A list of the neurodegenerative diseases associated with olfactory impairment associated discussed in this chapter is presented in Table.

OLFACTORY FUNCTION IN NEURODEGENERATIVE DISEASES

<hr/>	
Disease	Olfactory function
<hr/>	
disease	Impaired
Lewy body disease	Impaired
Familial Parkinson's disease (both IPD and PPS phenotypes)	Impaired
Progressive supranuclear palsy	Preserved

Multiple system atrophy	Mildly Impaired
Corticobasal ganglionic degeneration	Preserved
Parkinsonism-dementia of Guam	Impaired
MPTP-induced Parkinsonism	Preserved
Essential tremor	Mildly-moderately impaired
Alzheimer's disease	Impaired
Motor neuron disease	impaired/preserved
Huntington's disease	Impaired

OLFACTORY DYSFUNCTION IN THE CONTEXT OF CURRENT KNOWLEDGE OF NORMAL OLFACTION

The mechanism(s) underlying olfactory dysfunction in neurodegenerative diseases and normal aging have not yet been elucidated. However, a considerable body of information has accumulated over the last decade regarding the function of the olfactory system at the molecular, cellular, and system levels, both at the periphery and centrally. While several aspects of olfactory system function remain a mystery, a more complete understanding of the complex organization of the olfactory system is emerging from these analyses.

We now know that in the periphery, olfaction is initiated by binding of an odorous

ligand to the Ors that are expressed in olfactory neurons (ORN), located within the olfactory epithelium. The ORs reflect the first organizational level at which specificity is established, as each neuron expresses only one receptor type. The spatial organization of the neurons that express one type of receptor in the olfactory epithelium reflects the second organizational level at which specificity is established. The third level of organization occurs at the olfactory bulb where the second-order neurons form connections in specific stereotypic sites in the olfactory bulb. The axons of first order neurons from the heterogeneous fascicles that defasciculate in the olfactory bulb and refasciculate with neurons expressing the same OR. Both permissive and inhibitory cues may contribute to this organizational process. This axon targeting may constitute another level of organization. Finally, behaviorally induced plasticity in the olfactory bulb may add yet another level of organizational complexity⁶⁹. It will be important to understand whether the neurodegenerative process affects one or more levels of organization and the associated functions of the olfactory system

Since the establishment of an association of olfactory dysfunction with PD and other neurodegenerative diseases, two broadly crafted, alternate hypotheses have been proposed to account for the nature of the olfactory deficits. According to the first hypothesis, the observed olfactory impairment is due to peripheral processes such as environmental insults to the olfactory system. According to the second hypothesis, the olfactory impairment is due to central processes. Support for the second hypothesis is

provided by the the fact that in both PD and AD the olfactory system appears to be affected in a disease-specific manner. In patients with autopsy-proven PD, the AON contains dystrophic neuritis and Lewy bodies (LBs). These LB are morphologically more similar to cortical than to nigral LB⁷⁰. In addition, there is considerable neuronal loss in the AON. The degree of neuronal loss correlates strongly with the disease duration²⁴. This is in apparent contradiction with the observation that olfactory dysfunction is independent of disease duration in PD. In AD, neurofibrillary tangles and amyloid plaques are seen in the AON. PD-specific pathology is also observed in the amygdala⁶⁸. The amygdala is part of the limbic system and forms a large number of connections with the hippocampus and the entorhinal cortex as well as the neocortex. It is involved in memory , behavior, and regulation of endocrine and autonomic function and olfaction. In the amygdale, the neuropathological changes appear to accumulate slowly over time as the disease progresses. However, in PD patients, the severity of amygdale involvement appears to be independent of cognitive deficits⁶⁸.

Furthermore, the olfactory bulb is rich in dopamine neurons, and a physiological role for dopa in the olfactory bulb has been demonstrated in the rat olfactory system. Dopamine suppresses the electrical activity of mitral cells⁷¹, and the olfactory bulb is rich in dopamine receptors (both D1 and D2). In the olfactory bulb, there is a differential distribution pattern of the dopamine receptors⁷². Recently, it has been demonstrated that, in the rat olfactory bulb, dopamine receptor subtypes can modulate the response of

GABA A receptors and could be instrumental in odor detection, odor discrimination, and olfactory learning⁷³. Interestingly, in clinical studies, the olfactory dysfunction observed in PD appears not to be a manifestation of dopamine deficiency⁷⁴. Olfactory function was assessed in a small series of hyposmic PD patients before and after the administration of apomorphine, apotent, short acting dopamine agonist, and no difference was observed. While the number of parkinsonian individuals tested in the study was small, the fact that olfactory dysfunction appears to be independent of disease stage or duration³² provides indirect support for this hypothesis. However, this may be explained by the fact that the early appearance of symptoms of olfactory dysfunction may reflect a threshold phenomenon that is achieved earlier in the olfactory system than in other areas of the CNS.

The complexity of the olfactory system's organization and its extensive connections to many cortical regions, the basal ganglia, and cerebellum suggest that defects in any of a number of different molecular, cellular, or physiological processes may lead to olfactory dysfunction at the level of odor discrimination, recognition, and memory. In humans, many olfactory receptors genes (approximately 72%) are nonfunctional and are distributed on nearly all chromosomes. A large number of olfactory receptor genes are found in telomeric chromosomal regions⁷⁵. Given the association of telomere length with senescence⁷⁶ as well as the known association of olfactory dysfunction with aging, it is tempting to speculate that the telomeric location of

OR genes may make them more prone to deletion / inactivation that may in turn lead to age-dependent olfactory dysfunction. It is unclear whether such a process might play a role in the mechanisms underlying olfactory dysfunction associated with PD and neurodegenerative diseases.

System level approaches have provided a valuable perspective on the central mechanisms in the development and function of the olfactory system. It is thought that the brain can determine which neurons are excited by analyzing a topographic map in the olfactory bulb⁷⁸. Activity dependent mechanisms and stimulus specific synchronization of neuronal groups may be involved in olfactory processing^{79,80}. Network dynamics can also be instrumental by creating odour representation and optimizing their distribution. Both slow, nonperiodic processes and fast, oscillatory processes may contribute to the coding that is inherent in the olfactory system⁸¹. It will be important to understand whether and how these central mechanisms are altered in neurodegenerative disease.

CONCLUSIONS OF LITERATURE STUDY

The olfactory system is a complex network whose organization and function depends on both peripheral and central input. It is commonly affected in Parkinson's disease (PD), parkinsonism – plus syndromes (PPS), other neurodegenerative disorders (e.g., Alzheimer's disease, (AD)), and in normal aging. Olfactory dysfunction usually

appears early in the disease process. IN PD, olfactory function is commonly impaired whereas, in PPS, olfactory function is only mildly impaired or preserved. Olfactory function is also impaired in familial forms of parkinsonism associated with a monogenetic defect. In contrast to individuals with sporadic PPS, affected members of PPS kindreds do show olfactory impairment. Interestingly, olfactory dysfunction does not appear to be due to dopamine deficiency. The neuropathological changes in the olfactory system appear to be disease specific. This suggests that olfactory dysfunction in neurodegenerative disorders may reflect a central rather than a peripheral process. The organization of the normal olfactory system is gradually being elucidated at the molecular, cellular, and system levels. The mechanisms underlying olfactory dysfunction in PD and other neurodegenerative diseases remain unknown.

FUTURE DIRECTIONS

The study of the olfactory system in neurodegeneration offers a unique arena in which to employ a combination of analytical approaches at the molecular, cellular, physiological, and system levels. This uniqueness is not system-specific but rather, the result of simultaneous advances in many scientific fronts. An important advance is the identification of the primary genetic defect in a number of neurodegenerative disorders. Another important advance is the development of genomic and proteomic analyses in which the simultaneous expression of thousands of genes in different tissues including

brain tissue can be analyzed (e.g., using microarrays). Another advance is the analysis of the olfactory system by a dynamical system approach that has led to significant insights into the organization and complexity of olfactory system. Finally, the advent of functional imaging, including fMRI and PET, allows the in vivo functional characterization of olfaction and related higher cognitive processes in normal and diseased states. Understanding how the olfactory system is affected by neurodegeneration will require a synthesis of these conceptually different approaches. The field is in a particular moment in its development that a synthesis will open up new insights into both the functional understanding of the olfactory system as well as the neurodegenerative process.

AIMS OF THE STUDY

- 1) To assess the presence and the extent of olfactory impairment in various types of parkinsonian patients.
- 2) To assess the correlation between extent of olfactory dysfunction and the duration&severity of the disease in various types of parkinsonism.
- 3) To assess the practical use of olfactory function tests in supplementing the diagnosis of various parkinsonian syndromes
- 4) To assess any impact of DOPA therapy on olfactory impairment in various types of parkinsonism.

MATERIALS AND METHODS

This study was conducted among patients with various types of parkinsonism coming to outpatient clinic and in-patients of Institute of Neurology, Chennai over the period of 2 ½ years from Oct 2005 to March 2008. Seventy patients suffering from various types of parkinsonism were selected for olfactory functions tests in order to assess the presence and extent of olfactory dysfunction at various stages & duration of the illness and to analyse whether treatment will cause any change or improvement in olfactory functions.

INCLUSION CRITERIA

- 1) The patients who were presented with hypokinesia, rigidity with or without tremor in the age group of 20-75 years were included in this study.
- 2) Those patients who are having early signs and symptoms of parkinsonism within 5 years of duration of illness are included.
- 3) Patients with idiopathic parkinsonism, Progressive supranuclear palsy, Multi system atrophy, Familial parkinsonism, spinocerebellar atrophy presenting with parkinsonism and vascular parkinsonism are included.

EXCLUSION CRITERIA

- 1) Parkinsonian patients with more than 5 years duration of illness were excluded in order to avoid the confusion arising due to the presence of olfactory dysfunction commonly in late stages of parkinsonism of all types.
- 2) Patients with severe cognitive dysfunction&dementia were excluded because they cannot respond sensitively to the olfactory function tests and since the correct odour identification depends on the intact odour memory.
- 3) Patients with chronic upper respiratory tract infection like sinusitis,nasal polyp were excluded.
- 4) Patients with aphasia and parkinsonism were excluded because they will find it difficult to tell their inferences of olfactory function tests.
- 5) Patients >75 years of age were excluded because of the diminution of olfactory functions evolving naturally in old age people.
- 6) Parkinsonism due to secondary causes like Wilson's disease,Hallevordenspatz disease,Neuronal degeneration due to brain iron accumulation,Huntington's disease, some mitochondrial diseases presenting with parkinsonism,neuroleptic drug induced parkinsonism and parkinsonism with florid psychiatric manifestations were excluded

A total of 70 cases of parkinsonism belonging to various subtypes were selected according to the inclusion&exclusion criteria,thoroughly examined clinically and investigated with blood chemistry and CT&MRI scans.Patients with idiopathic parkinsonism are categorized according to UPDRS scoring and Modified Hoehn&Yahr

staging.

All the 70 patients are analysed by 1) odour identification test, 2) odour discrimination Test & 3) odour threshold test. This prospective observational study was done serially once in 3 months for every patient for a total period of one year.

The odourous substances used in this study are the following

1) coffee powder 2) Tea powder 3) Camphor 4) Tobacco powder 5) Asafoetida 6) Pepper powder 7) coriander leaves (mashed) 8) eucalyptus oil 9) jasmine flowers 10) Rose petals 11) antiseptic spirit and 12) naphthalene balls.

Only 12 odorous substances were used in order to simplify the testing and to reduce the time taken to complete the entire olfactory testing.

Every patient was instructed to close both eyes and asked to sniff gently the given odorous substance kept in a small bowl in each nostril separately by closing the other nostril. One minute time was given to identify the odour and the patient was asked to choose the correct item from the 4 written answers.

If the patient identified >10 substances-normal. 8-10 (mild olfactory dysfunction)

5-7(moderate olf.dysfunction),0-4(severe olf.dysfunction)

Sl.no	Scoring of the Olfactory dysfunction	Number of odourous substances identified (Out of 12 substances)
1	Mild	8-10
2	Moderate	5-7
3	Severe	0-4

Odour discrimination test was performed by giving 2 different odourous substances and third odour similar to the first odourous substance and the patient was asked to differentiate the odours correctly.

Odour threshold testing was performed by giving various dilutions of n-butyl alcohol starting from low dilutions to slowly increasing dilutions(upto 4% max.dilution) and the dilution of alcohol at which patient starts to appreciate the odour was identified.

The presence&severity of olfactory dysfunction was analysed in various subtypes of parkinsonian patients and was correlated with different stages of parkinsonism and duration of illness.

New patients with Idiopathic parkinsonism, Multiple system atrophy and Progressive supranuclear palsy were started on adequate dopa therapy and the old patients were maintained on their previous treatment schedule(dopa and anticholinergics).

Modified Hoehn and Yahr staging of Parkinson's disease

Stage 0-no signs of the disease

Stage 1-Unilateral disease

Stage 1.5-Unilateral plus axial involvement

Stage 2-Bilateral disease,without impairment of balance

Stage 2.5-Mild bilateral disease with recovery on pull test

Stage3-Mildto moderate bilateral disease,some postural instability,physically independent

Stage 4-Severe disability,still able to walk or stand unassisted

Stage 5-Wheel chair bound or bedridden unless aided.

Unified Parkinson's Disease Rating Scale (UPDRS)

The UPDRS is a rating tool to follow the longitudinal course of Parkinson's Disease. It is made up of the 1) Mentation, Behavior and Mood 2)ADL and 3) Motor

sections. These are evaluated by interview. Some sections require multiple grades assigned to each extremity. A total of 176 points are possible. 176 represents the worst (total) disability), 0—no disability.

I. Mentation, Behavior & Mood

Intellectual Impairment

0-none.

1-mild (consistent forgetfulness with partial recollection of events)

2-moderate memory loss with disorientation and moderate difficulty handling complex problems.

3-severe memory loss with disorientation to time and often place, severe impairment with problems.

4-severe memory loss with orientation only to person, unable to make judgments or solve problems.

Thought Disorder

0-none

1-vivid dreaming

2-"benign" hallucination with insight retained

3-occasional to frequent hallucination or delusions without insight

4-persistent hallucination, delusions, or florid psychosis.

Depression

0-not present

1-periods of sadness or guilt greater than normal, never sustained

- more than a few days or a week
- 2-sustained depression for >1 week
- 3-vegetative symptoms (insomnia, anorexia, abulia, weight loss)
- 4-vegetative symptoms with suicidality

Motivation/Initiative

- 0-normal
- 1-less of assertive, more passive
- 2-loss of initiative or disinterest in elective activities
- 3-loss of initiative or disinterest in day to say (routine) activities
- 4-withdrawn, complete loss of motivation

II. Activities of Daily Living

Speech

- 0-normal
- 1-mildly affected, no difficulty being understood
- 2-moderately affected, may be asked to repeat
- 3-severely affected, frequently asked to repeat
- 4-unintelligible most of time

Salivation

- 0-normal
- 1-slight but noticeable increase, may have nighttime drooling
- 2-moderately excessive saliva, hay minimal drooling
- 3-marked drooling

Swallowing

- 0-normal
- 1-rare choking

2-occasional choking

3-requires soft food

4-requires NG tube or G-tube

Handwriting

0-normal

1-slightly small or slow

2-all words small but legible

3-severely affected, not all words legible

4-majority illegible

Cutting Food/Handing Utensils

0-normal

1-somewhat slow and clumsy but no help needed

2-can cut most foods, some help needed

3-food must be cut, but can feed self

4-needs to be fed

Dressing

0-normal

1-somewhat slow, no help needed

2-occasional help with buttons or arms in sleeves

3-considerable help required but can do something alone

4-helpless

Hygiene

0-normal

1-somewhat slow but no help needed

2-needs help with shower or bath or very slow in hygienic care

3-requires assistance for washing, brushing teeth, going to bathroom

4-helpless

Turning in Bed/ Adjusting Bed Clothes

0-normal

1-somewhat slow no help needed

2-can turn alone or adjust sheets but with great difficulty

3-can initiate but not turn or adjust alone

4-helpless

Falling-Unrelated to Freezing

0-none

1-rare falls

2-occasional, less than one per day

3-average of once per day

4->1 per day

Freezing When Walking

0-normal

1-rare, may have start hesitation

2-occasional falls from freezing

3-frequent freezing, occasional falls

4-frequent falls from freezing

Walking

0-normal

- 1-mild difficulty, day drag legs or decrease arm swing
- 2-moderate difficulty requires no assist
- 3-severe disturbance requires assistance
- 4-cannot walk at all even with assist

Tremor

- 0-absent
- 1-slight and infrequent, not bothersome to patient
- 2-moderate, bothersome to patient
- 3-severe, interfere with many activities
- 4-marked, interferes with many activities

Sensory Complaints Related to Parkinsonism

- 0-none
- 1-occasionally has numbness, tingling, and mild aching
- 2-frequent, but not distressing
- 3-frequent painful sensation
- 4-excruciating pain

III. Motor Exam

Speech

- 0-normal
- 1-slight loss of expression, diction, volume
- 2-monotone, slurred but understandable, mod. impaired
- 3-marked impairment, difficult to understand
- 4-unintelligible

Facial Expression

- 0-Normal

- 1-slight hypomymia, could be poker face
- 2-slight but definite abnormal diminution in expression
- 3-mod. hypomimia, lips parted some of time
- 4-masked or fixed face, lips parted 1/4 of inch or more

*Tremor at Rest

Face

- 0-absent
- 1-slight and infrequent
- 2-mild and present most of time
- 3-moderate and present most of time
- 4-marked and present most of time

Right Upper Extremity & Left upper extremity

- 0-absent
- 1-slight and infrequent
- 2-mild and present most of time
- 3-moderate and present most of time
- 4-marked and present most of time

Right lower extremity & Left lower extremity

- 0-absent
- 1-slight and infrequent
- 2-mild and present most of time
- 3-moderate and present most of time
- 4-marked and present most of time

*Action or Postural Tremor

Right upper extremity & Lt upper extremity

- 0-absent

- 1-slight, present with action
- 2-moderate, present with action
- 3-moderate present with action and posture holding
- 4-marked, interferes with feeding

*Rigidity

Neck

- 0-absent
- 1-slight or only with activation
- 2-mild/moderate
- 3-marked, full range of motion
- 4-severe

Right upper extremity&Left upper extremity

- 0-absent
- 1-slight or only with activation
- 2-mild/moderate
- 3-marked, full range of motion
- 4-severe

Right lower extremity&Left lower extremity

- 0-absent
- 1-slight or only with activation
- 2-mild/moderate
- 3-marked, full range of motion
- 4-severe

*Finger taps

Right&Left finger taps

- 0-normal
- 1-mild slowing, and/or reduction in amp.

- 2-moderate impaired. Definite and early fatiguing,
- 3-severely impaired. Frequent hesitations and arrests.
- 4-can barely perform

***Hand Movements (open and close hands in rapid succession)**

Right & Left hand movements

- 0-normal
- 1-mild slowing, and/or reduction in amp.
- 2-moderate impaired. Definite and early fatiguing
- 3)severely impaired. Frequent hesitations and arrests.
- 4-can barely perform

***Rapid Alternating Movements (pronate and supinate hands)**

Right&Left hands

- 0-normal
- 1-mild slowing, and/or reduction in amp.
- 2-moderate impaired. Definite and early fatiguing,
- 3-severely impaired. Frequent hesitations and arrests.
- 4-can barely perform

***Leg Agility (tap heel on ground, amp should be 3 inches)**

Right&Left leg

- 0-normal
- 1-mild slowing, and/or reduction in amp.
- 2-moderate impaired. Definite and early fatiguing,
- 3-severely impaired. Frequent hesitations and arrests.
- 4-can barely perform

***Arising From Chair**

- 0-normal

- 1-slow, may need more than one attempt
- 2-pushes self up from arms or seat
- 3-tends to fall back, may need multiple tries but can arise without assistance
- 4-unable to arise without help

***Posture**

- 0-normal erect
- 1-slightly stooped, could be normal for older person
- 2-definitely abnormal, mod. stooped, may lean to one side
- 3-severely stooped with kyphosis
- 4-marked flexion with extreme abnormality of posture

***Gait**

- 0-normal 1-walks slowly, may shuffle with short steps, no festination
- 2-walks with difficulty, little or no assistance, some festination, short steps
- 3-severe disturbance, frequent assistance
- 4-cannot walk

***Postural Stability (retropulsion test)**

- 0-normal
- 1-recovers unaided
- 2-would fall if not caught
- 3-falls spontaneously
- 4-unable to stand

***Body Bradykinesia/ Hypokinesia**

- 0-none
- 1-minimal slowness, could be normal, deliberate character
- 2-mild slowness and poverty of movement, definitely abnormal
- 3-moderate slowness, poverty, or small amplitude

4-marked slowness, poverty, or amplitude

Grades of UPDRS scoring

Mild disease-score 1-31

Moderate disease score 32-62

Severe disease 63-176

RESULTS OF THE STUDY

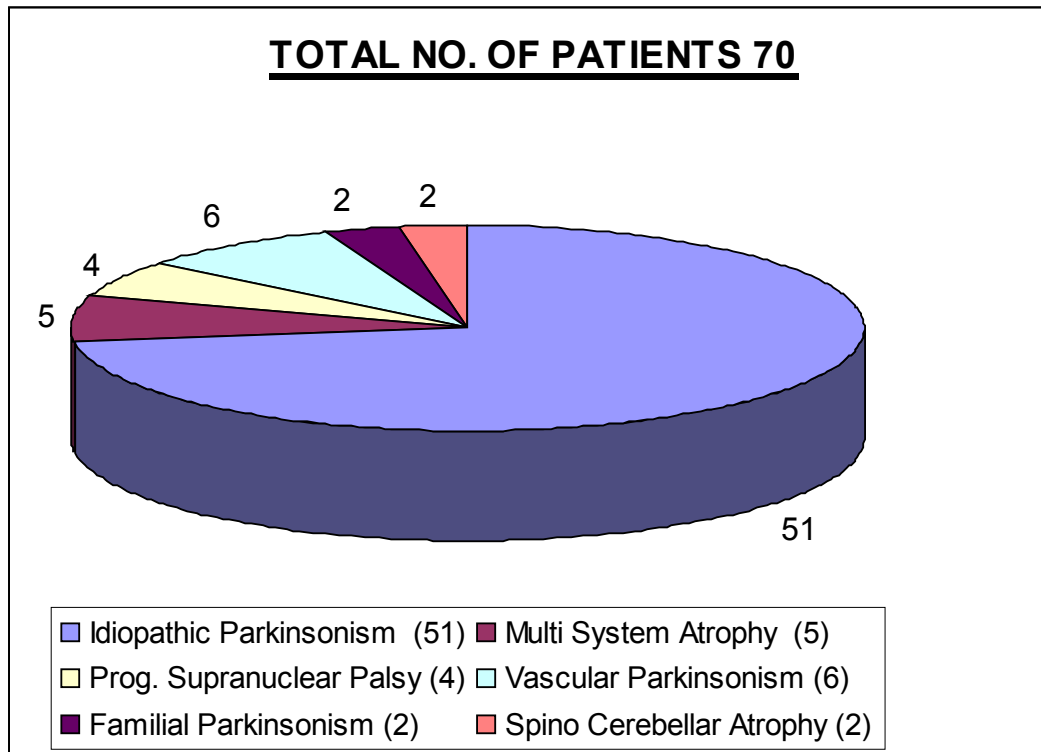
Out of 70 patients with parkinsonism, 52 patients were males, 18 patients were females. 51 patients are of Idiopathic parkinsonism, 5 patients are of Multiple system atrophy, 4 patients are of Progressive supranuclear palsy, 6 patients are of vascular parkinsonism, 2 patients are of Spinocerebellar ataxia and 2 patients are of familial parkinsonism.

Number of patients with various subtypes of parkinsonism studied

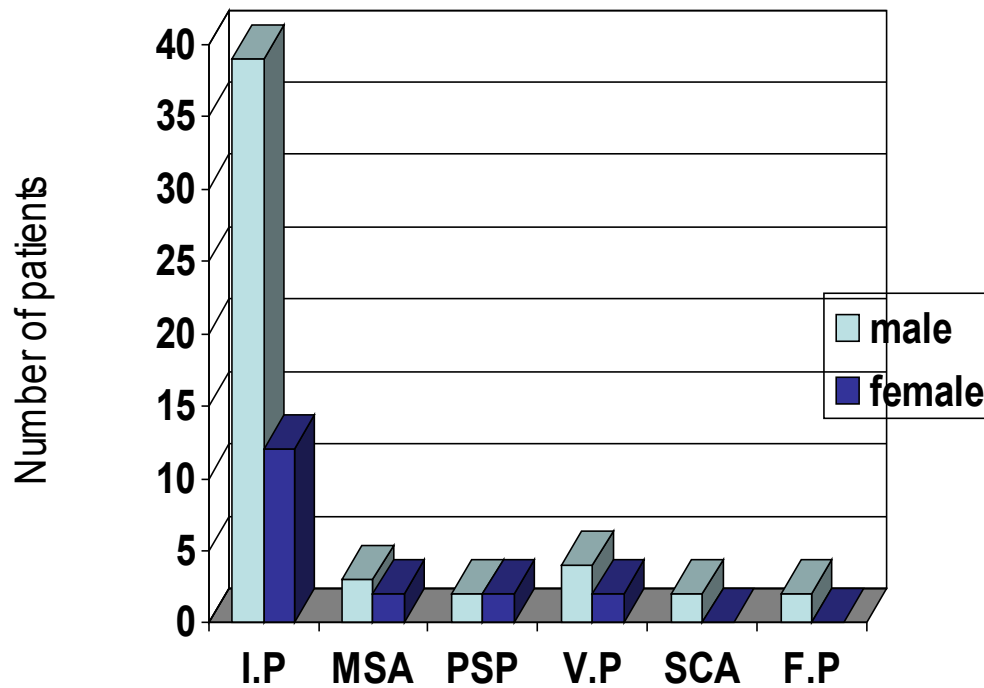
	Type of Parkinsonism	Male	Female	Total	Percentage(out of 70 patients)
1	Idiopathic Parkinsonism	39	12	51	72.8%
2	Multi system Atrophy	3	2	5	7%
3	Prog. supranuclear palsy	2	2	4	5.5%
4	Vascular Parkinsonism	4	2	6	8.6%
5	Familial Parkinsonism	2	0	2	2.9%
6	SCA(with parkinsonism)	2	0	2	2.9%
Total		52	18	70	100%

NUMBER OF PATIENTS WITH VARIOUS SUBTYPES OF PARKINSONISM

STUDIED



Number of patients with various types of parkinsonism presented in this study



I.P-Idiopathic parkinsonism,MSA-Multisystem atrophy,
PSP-Progressive supranuclear palsy,V.P- Vascular parkinsonism,
SCA-Spinocerebellar atrophy,F.P-Familial parkinsonism

Age spectrum of patients presented with various types of parkinsonism

	Type of Parkinsonism	21-30yrs	31-40yrs	41-50yrs	51-60yrs	61-70yrs	71-75yrs
1	Idiopathic Parkinsonism	--	--	9	14	19	9
2	Multisystem Atrophy	--	--	3	2	--	--
3	Progressive supranuclear palsy	--	--	3	1	--	--
4	Vascular Parkinsonism	--	--	--	1	3	2
5	Familial Parkinsonism	--	1	1	--	--	--
6	SCA(with parkinsonism)	2	--	--	--	--	--
	Total(70 patients)	2	1	16	18	22	11

Patients with parkinsonism presented at various duration of illness

	Types of Parkinsonism	1 st yr	2 nd yr	3 rd yr	4 th yr	5 th yr
1	Idiopathic Parkinsonism	24	14	7	6	--
2	Multi system Atrophy		3	1	1	1
3	Progressive supranuclear palsy	1	--	1	2	--
4	Vascular Parkinsonism	2	3	1	--	--
5	Familial Parkinsonism	--	1	1	--	--
6	SCA(with parkinsonism)	--	--	--	1	--
	Total	27	21	11	10	1

UPDRS scoring of Idiopathic Parkinsonism patients

Mild(1-31score)		Moderate(32-62score)		Severe(63-176score)	
male	Female	male	female	Male	female
26	8	10	3	3	1
Total	34	13		4	

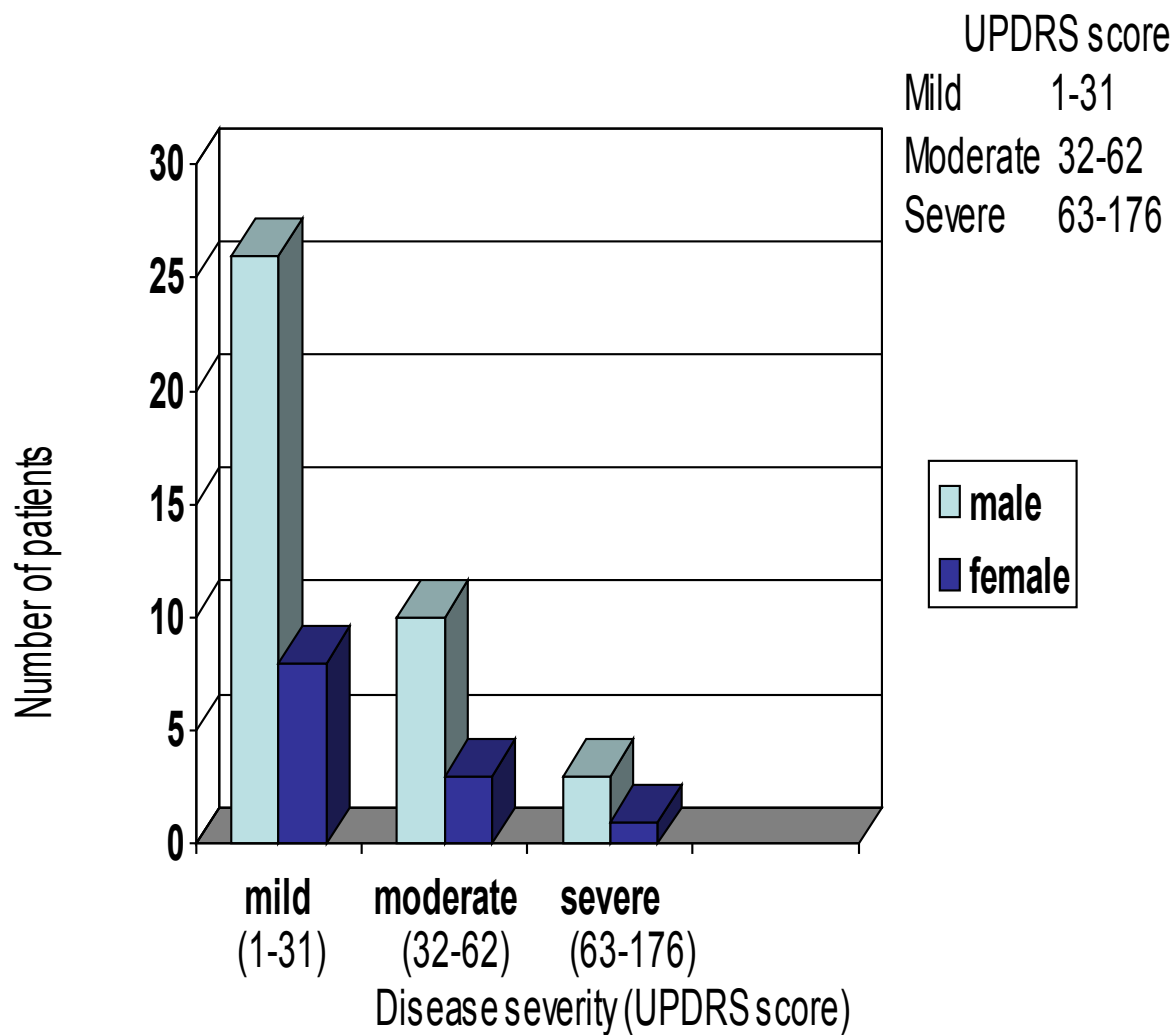
Number of patients with idiopathic parkinsonism(Hoehn&Yahr staging)

	Hoehn&Yahr staging	Male	Female	Total
1	Stage 1	6	3	9
2	Stage 1.5	5	1	6
3	Stage 2	11	3	14
4	Stage 2.5	4	1	5
5	Stage 3	10	3	13
6	Stage 4	3	1	4
7	Stage 5	0	0	0

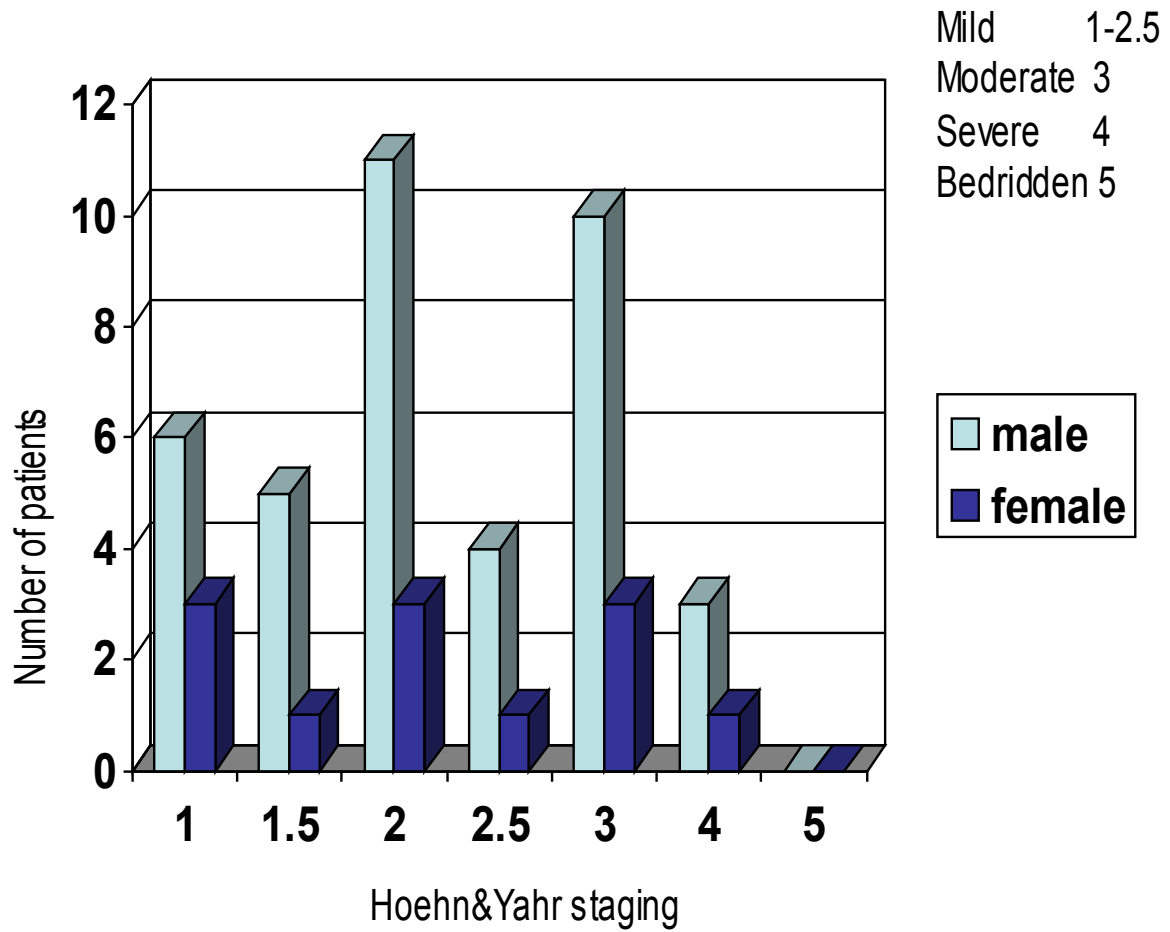
Net results of olfactory function tests in various types of parkinsonism patients

	Types of Parkinsonism	Total number of cases	Patients with olfactory dysfunction			percentage
			Odour Identificatin impairment	Odour discriminatin impairment	Odour threshold elevation	
1	Idiopathic parkinsonism	51	51	51	51	100%
2	Multisystem atrophy	5	2	2	0	40%
3	Prog.supranuclear palsy	4	0	0	0	0%
4	Familial parkinsonism	2	2	2	2	100%
5	Vascular parkinsonism	6	0	0	0	0%
6	SCA	2	0	0	0	0%

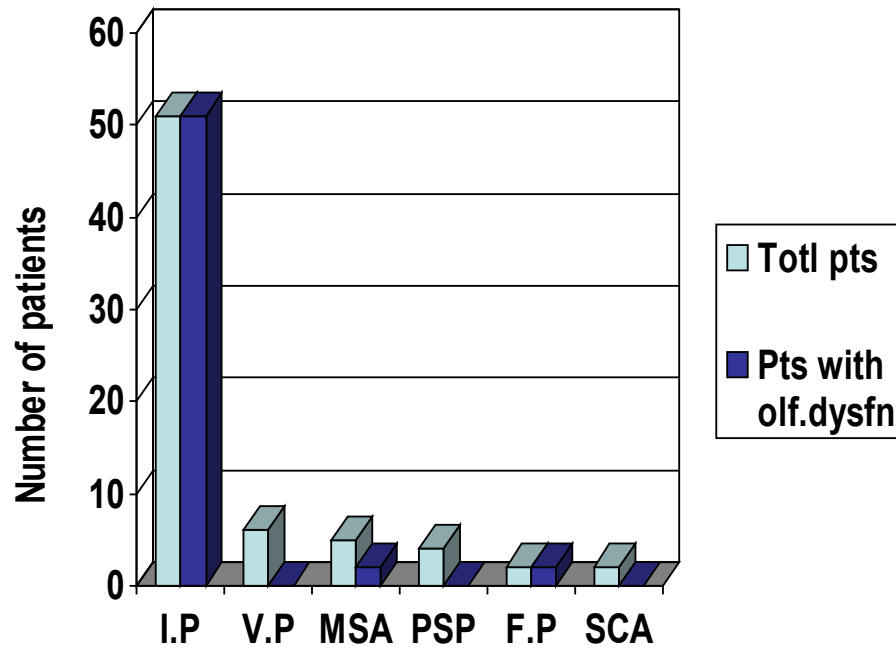
UPDRS grading of 51 idiopathic parkinsonian patients



Hoehn&Yahr staging of 51 idiopathic parkinsonian patients



Olfactory dysfunction in various subtypes of parkinsonism

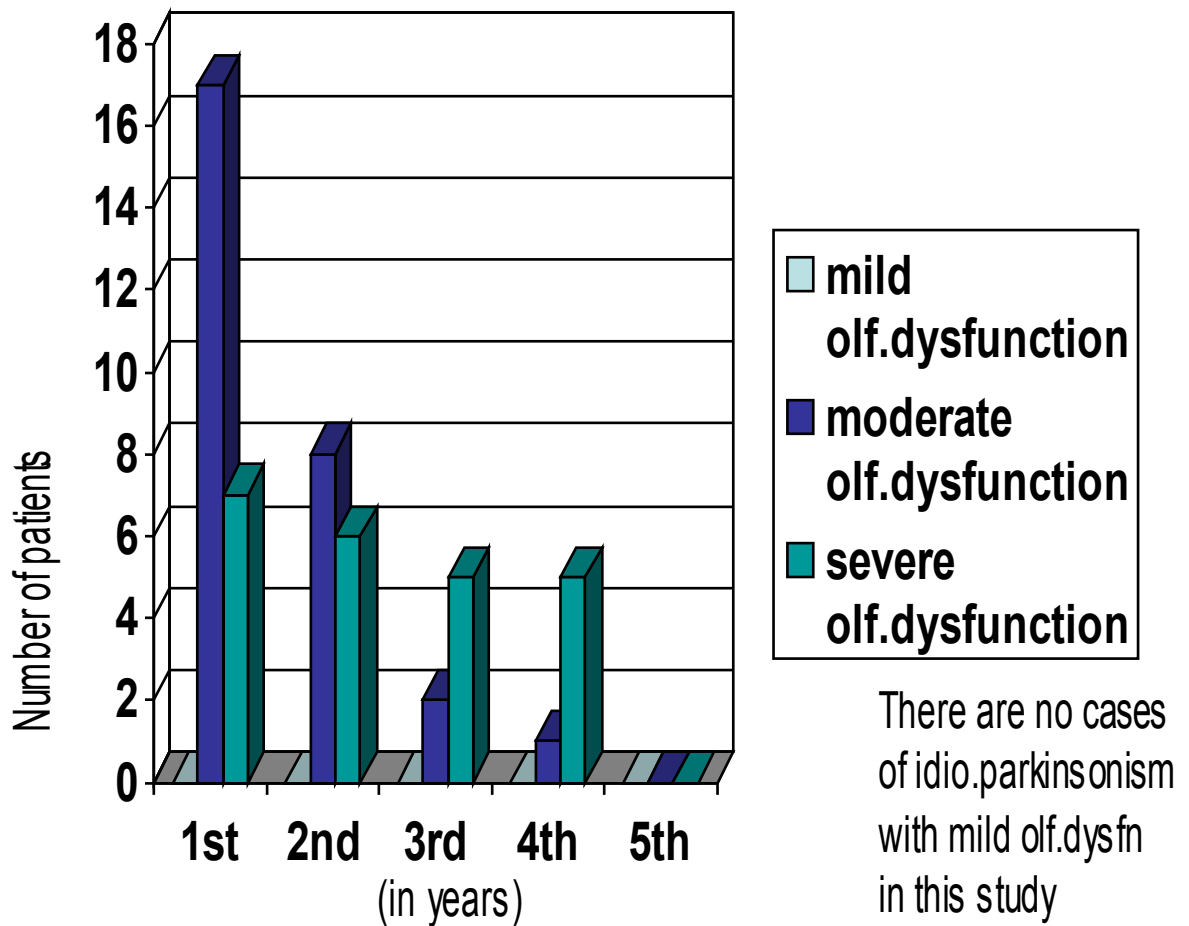


I.P-Idiopathic parkinsonism,V.P-Vascular parkinsonism
MSA-Multisystem atrophy,PSP-Prog.supranuclear palsy
F.P-Familial parkinsonism,SCA-Spinocerebellar atrophy

Results of olfactory function tests in various types of parkinsonism patients

		Severity of Olfactory dysfunction correlated with Duration of illness															T O T A L
Duration of illness		1 st yr			2 nd yr			3 rd yr			4 th yr			5 th yr			
Types of Parkinsonism		O L F A			C T O R			Y D Y S			F U N C			T I O N			
		mil	mod	sev	mil	mod	sev	mil	mod	sev	mil	mod	sev	mil	mod	sev	
1	Idio. Parkinsonism	--	17	7	--	8	6	--	2	5	--	1	5	--	--	--	51
2	Multi system atrophy	--	--	--	--	--	--	--	--	--	1	--	--	1	--	--	2
3	Prog.supranu.palsy	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	0
4	Familial parkinsonism	--	--	--	1	--	--	--	1	--	--	--	--	--	--	--	2
5	Vascular parkinsonism	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	0
6	SCA	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	0

Severity of olfactory dysfunction in idiopathic parkinsonian pts at various duration of illness



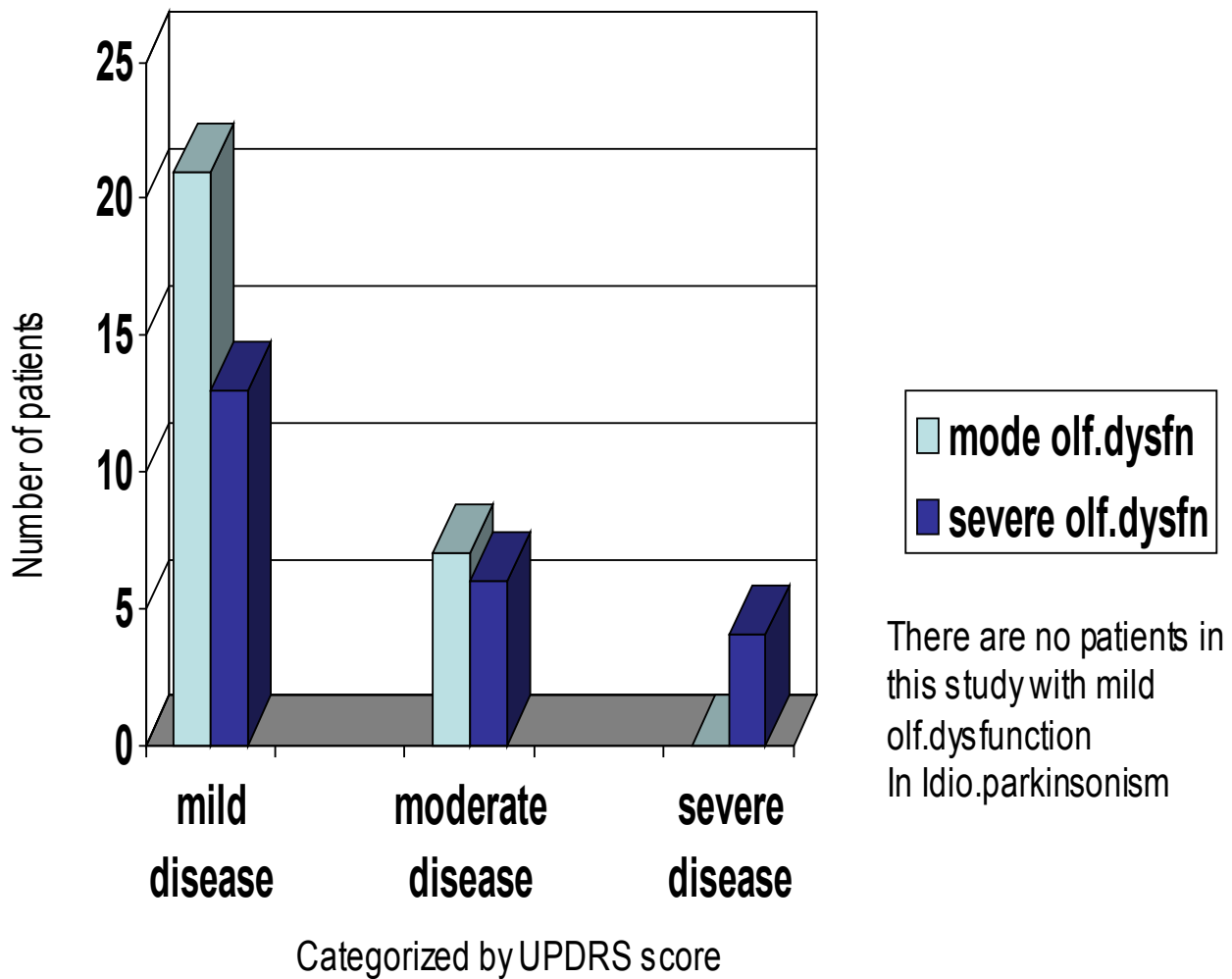
Results of olfactory functions tests in idiopathic parkinsonism patients
(categorized according to UPDRS scoring)

	Severity of parkinsonism UPDRS scoring category	Impairment of odour identification			Impairment of Odour discrimination	Odour threshold elevation
		Mild(able to identify 8-10 items)	Moderate (able to identify 5-7 items)	Severe (able to identify 0-4 items only)		
1	Mild disease (out of 34 patients)	0	21	13	34	34
2	Moderate disease (out of 13 patients)	0	7	6	13	13
3	Severe disease (out of 4 patients)	0	0	4	4	4
	Total	0	28	23	51	51

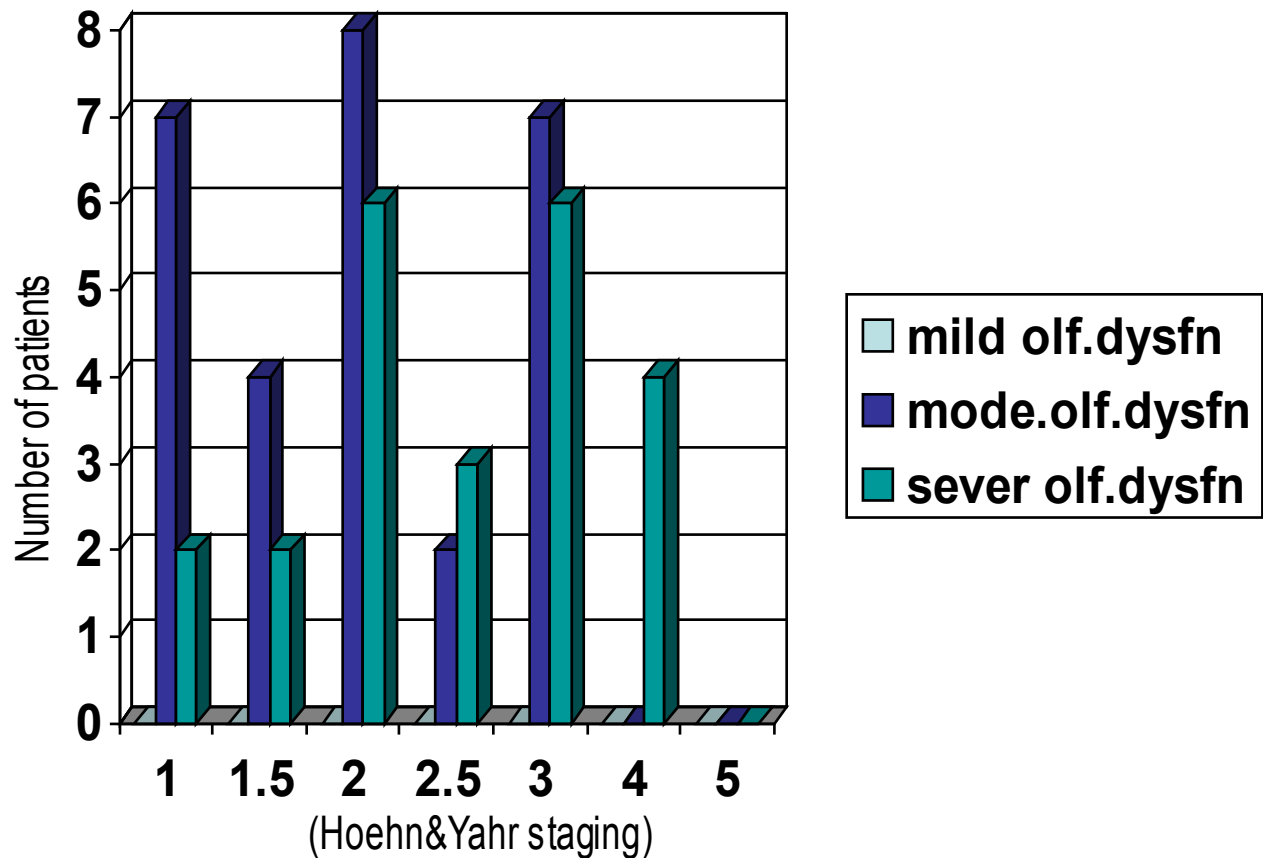
Results of olfactory function tests in idiopathic parkinsonism patients
(categorized by Hoehn & Yahr staging)

	Hoehn&Yahr staging	Olfactory function impairment				
		Odour identification impairment			Odour discrimination impairment	Odour threshold test(elevated)
		mild	moderate	severe		
1	Stage 1 (9 patients)	0	7	2	9	9
2	Stage 1.5 (6 patients)	0	4	2	6	6
3	Stage 2 (14 patients)	0	8	6	14	14
4	Stage 2.5 (5 patients)	0	2	3	5	5
5	Stage 3 (13 patients)	0	7	6	13	13
6	Stage 4 (4 patients)	0	0	4	4	4
7	Stage 5 (0 patients)	0	0	0	0	0

Olfactory dysfunction in Idiopathic parkinsonism patients
categorized by UPDRS score



Olfactory dysfunction in various stages of Idio.parkinsonism patients (categorized by Hoehn&Yahr staging)



Gross results of olfactory function tests in various types of parkinsonism patients

	Olfactory tests	I.P	MSA	PSP	V.P	F.P	SCA
1	Odour identification	severely Impaired	Mildly impaired	Normal	Normal	Moderately Impaired	Normal
2	Odour discrimination	severely Impaired	Mildly impaired	Normal	Normal	Moderately Impaired	Normal

3	Odour threshold	elevated	normal	Normal	Normal	elevated	Normal
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I.P-Idiopathic Parkinsonism,MSA-Multisystem atrophy,PSP-Progressive supranuclear palsy,V.P-Vascular parkinsonism,F.P-Familial parkinsonism,SCA-Spinocerebellar ataxia

RESULTS OF THE OLFACTORY FUNCTION TESTS

Out of 70 patients with parkinsonism tested in this study,51patients (72.8%)are of idiopathic parkinsonism,5patients(7%) are of MSA,4patients(5.5%) are of PSP,6patients (8.6%)are of vascular parkinsonism,2patients(2.9%) are of familial parkinsonism and 2 patients(2.9%) are of SCA.Among 70 patients studied,52 are males,18 are females making M:F ratio almost 3:1.

- 1) In 51patients with idiopathic parkinsonism,Odour identification test showed that 28 patients had moderate olfactory dysfunction,23 patients had severe olfactory dysfunction and all 51 patients also had impaired odour discrimination and elevated odour threshold.
- 2) 24 patients presented themselves in the first year of their illness.Among these pts,7

patients have already severe olfactory dysfunction and 17 patients had moderate olfactory dysfunction. Out of 14 pts presented in 2nd year of their illness, 6 patients had severe olfactory dysfunction, 8 patients had moderate olfactory dysfunction. Out of 7 pts presented in 3rd year of illness, 5 patients had severe and 2 patients had moderate olf. dysfunction. Out of 6 patients presented in 4th year of illness, 5 patients had severe olf. dysfunction and one patient had moderate olf. dysfunction.

- 3) In 51 idiopathic parkinsonian patients, 6 patients showed strictly unilateral signs in the form of tremor and rigidity, 22 patients showed bilateral but asymmetrical signs and the remaining 23 patients showed bilateral symmetrical signs. But all 51 patients had bilateral olfactory impairment irrespective of the asymmetrical signs in many of them.
- 4) In 5 MSA patients, 2 patients (one presented at 4th year and another presented at 5th year of illness) had mild olf. dysfunction.
- 5) Out of 2 familial parkinsonism patients, One presented at 2nd year of illness had mild olf. dysfunction and the other presented at 3rd year of illness had moderate olf. dysfunction
- 6) In all PSP (4 patients), Vascular parkinsonism (6 patients) and SCA (2 patients)

cases, None had olfactory dysfunction.

All newly diagnosed patients were started on L.Dopa and anticholinergics therapy and the dopa therapy given to the already diagnosed patients were maintained with minimal modifications of dosage if needed.

Periodical followup olfactory function tests of all patients were done at every 3 months for a minimum period of one year.

The results of olfactory function tests at the end of one year.

1) In Idiopathic parkinsonism patients, out of 28 patients with moderate olfactory dysfunction, 16 patients deteriorated further to have severe olfactory dysfunction in spite of continued Dopa therapy. These 16 patients have deteriorated further in the severity of the illness (from H&Y staging 2-2.5 to 3-4). Those patients with severe olfactory dysfunction (23 patients) continued to have severe olf. dysfunction in spite of treatment with L.Dopa.

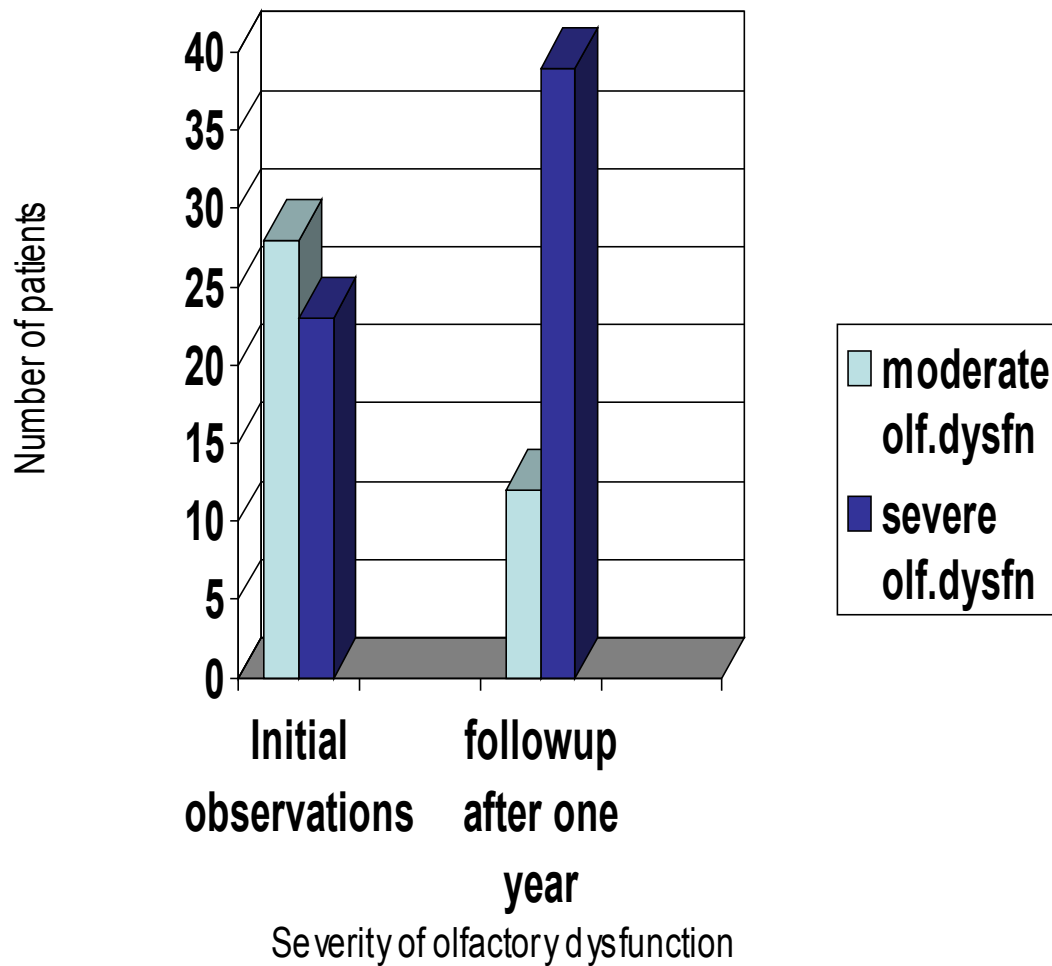
Changes in olfactory impairment of Idiopathic Parkinsonism patients in the followup study after one year

Severity of olf.dysfunction	Initial observations			Followup after one year		
	H&Y staging	number of patient	Total number of patient	H&Y staging	Number of patients	Total number of patient
Moderate olfactory dysfunction	Stage 1	4	28	Stage1	1	12
	Stage1.5	6		Stage1.5	3	
	Stage2	12		Stage2	3	
	Stage2.5	6		Stage2.5	5	
	Stage3	0		Stage3	0	
	Stage4	0		Stage4	0	
Severe olfactory dysfunction	Stage1	0	23	Stage1	0	39
	Stage1.5	0		Stage1.5	0	
	Stage2	0		Stage2	0	
	Stage2.5	0		Stage2.5	0	
	Stage3	16		Stage3	26	
	Stage4	7		Stage4	13	

- 2) Out of 2 patients with familial parkinsonism, One patient who had mild olf.dysfunction worsened to have moderate olf.dysfunction at the end of one year inspite of Dopa therapy and the other patient who had moderate olf.dysfunction earlier remained static as before.

- 3) Out of 5 patients with MSA, the two patients who had mild olfactory dysfunction continued to have mild olf.dysfunction inspite of further worsening of their illness and the three patients

Olfactory dysfunction after one year followup in Idio.parkin pts
compared with initial observations



who didn't have any olf.dyfunction earlier continued to have normal
olf.dysfunction at the end of one year.

- 4) In all patients with PSP,SCA,Vascular parkinsonism who participated in this study(PSP-4cases,SCA-2cases,Vascular parkinsonism-6cases),whose olfactory functions were normal at the beginning of the study remained so at the end of one year.

DISCUSSION

- 1) The results of the olfactory function tests done in 70 patients with various types of Parkinsonism showed that all patients with idiopathic parkinsonism had moderate to severe olfactory dysfunction in the form of impaired odour identification & discrimination and elevated odour threshold. These observations are similar to the results shown by Meshulam et al study³¹(1987).
- 2) The study results showed that olfactory impairment is more severe in later stages of parkinsonism(H&Y stage 3-5)(UPDRS score 63-176). The severity of olfactory impairment is not depending on the duration of illness because 7 patients had severe olfactory impairment in their first year of illness itself with disease severity ranging from H&Y stage 3-4 and 17 patients had moderate olfactory impairment in their first year of illness with disease severity ranging from H&Y stage 1-2.5. It shows clearly that in Idiopathic parkinsonism patients, the olfactory impairment already exists very early in the disease course and the severity of olfactory impairment worsens further in H&Y stages 3-4. These observations are exactly similar to the results shown by Doty et al³² and Stern et al³³ study where it was observed that olfactory dysfunction is independent of the disease duration and is more impaired in advanced Parkinson's disease(H&Y stage 3 or more).

- 3) Doty^{9,10} and Hawkes et al⁷⁰ found out in their studies that 70-100% of their patients with idiopathic parkinsonism had olfactory impairment thus making this as common a clinical sign as a pill rolling rest tremor. In this study, all 51 patients (100%) of idiopathic parkinsonism had moderate to severe olfactory impairment that too many of them had it in their early phases of illness.
- 4) Stern and Doty et al³⁵ found out that the olfactory impairment in idiopathic parkinsonian patients occurs bilaterally even when motor signs are asymmetrical or unilateral and it is independent of anti parkinsonian medication and does not vary between the “on-off” state in Dopa treated patients. In this study, out of 51 idiopathic parkinsonian patients, 6 patients had strictly unilateral signs in the form of tremors and rigidity and 22 patients had bilateral asymmetrical signs but all of them had bilateral olfactory impairment and the olfactory tests conducted at the “on-off” state due to dopa therapy in some of these patients showed same olfactory impairment in these two states without any changes. All these observations correlates well with findings made out by Stern and Doty et al.
- 5) In the followup study, 16 patients had further worsening of olfactory impairment (from moderate to severe) with worsening of severity of the illness. In the remaining 12 patients who had the same moderate olfactory impairment after one year, the disease severity has not changed. It again clearly indicates the more

worsening of olfactory impairment occurs in the later stages of idiopathic parkinsonism(H&Y staging 3-5) irrespective of duration of the disease. Also the study results showed that there is no improvement observed in olfactory functions after L.Dopa therapy. Doty and Stern et al³⁵ study showed similar results.

So the olfactory dysfunction in Idiopathic parkinsonism patients is not dependent on disease duration and therapy but it is present in the early stage of the illness and is more severe in late stages of the parkinsonism.

- 6) In 2 cases of Familial parkinsonism(all other secondary causes of parkinsonism were ruled out),there are moderate olfactory dysfunction with disease severity for one person H&Y stage 2.5 and for another stage3.Unfortunately,it was not possible to test olfactory functions in all the family members due to the non reporting of the family members to the hospital inspite of repeated requests.The observations made in familial parkinsonism patients are similar to the results shown in Markopoulou et al study^{43,44}.
- 7) In 5 MSA cases studied,2 cases had mild olfactory dysfunction when they presented at 4th and 5th year of their illness with the disease severity of H&Y stage 3 and 4 respectively.One year followup study showed there was no further worsening of olfactory dysfunction inspite of increasing disease severity.The

remaining cases did not show any olfactory dysfunction even after one year followup inspite of worsening illness.Muller et al⁴¹study(2002) showed similar results in MSA group of patients.

- 8) In 4 cases of PSP,6 cases of Vascular parkinsonism and 2 cases of SCA(SCA1&SCA3 presenting with parkinsonism),None had olfactory dysfunction.Even after one year followup,none developed olfactory dysfunction.These observations are similar to the results shown by Wenning and Doty et al^{38,39} study done in atypical parkinsonism patients.

Based on the above study results,one can be definite to diagnose idiopathic parkinsonism even at the earliest stage of the disease when the diagnosis is doubtful,if the patient is found out to have significant olfactory impairment.

CONCLUSIONS

Significant olfactory impairment is present even in early stages of idiopathic parkinsonism

- 1) Odour identification and odour discrimination are both impaired and odour threshold is elevated in idiopathic parkinsonism.
- 2) Olfactory impairment is severe in later stages of Idiopathic parkinsonism.
- 3) The severity of olfactory impairment is not dependent on the duration of illness but dependant on the disease stage(Hoehn&Yahr staging and UPDRS scoring)
- 4) In doubtful early clinical presentation of parkinsonism,presence of significant olfactory impairment suggests the possibility of Idiopathic parkinsonism.
- 5) Dopa therapy does not alter the presence or severity of olfactory impairment in various subtypes of parkinsonism.
- 6) In Familial parkinsonism,olfactory functions are impaired.
- 7) In Multi system atrophy,olfactory functions are impaired mildly in late stages of illness.

In Progressive supranuclear palsy,Vascular parkinsonism,

Spinocerebellar ataxia presenting with parkinsonism,olfactory functions are not impaired.

- 8) Olfactory function tests can be used as an easy bedside supplementary clinical tool in the diagnosis of various subtypes of parkinsonism.

PROFORMA FOR EVALUATION

The seventy patients who were presented with hypokinesia, rigidity with or without tremors were thoroughly examined clinically according to the proforma given below.

Name	Age	sex	occupation
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Complaints	Duration
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Present History

Slowness of activities	Tendency to fall	Tremors of hands/body/head
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Laterality of symptoms (uni or bilateral)

Cognition level	Emotional attitude	speech difficulty
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Symptoms of associated systems involvement

Pyramidal	cerebellar	autonomic
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Duration of each & every symptom

Past History

Hypertension	Exposure to industrial toxins, pesticides, CO
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Diabetes	Smoking
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Hyperlipidaemia

Alcoholism,Psychosis&Treatment

Previous strokes

Family history of similar illness

Head injury

Sinusitis(to do olfactory function tests)

Clinical examination

Higher mental functions

Cognition level

Speech

Apraxia

Memory

Behaviour

Psychiatric illness

Cranial nerves examination

Pupils

fundus

K.F.ring

Saccades pursuit gaze palsy mask like facies blink rate jaw jerk

Release reflexes glabellar palmomental snout

Spino motor system

Bulk tone(cog wheel,leadpipe,axial rigidity) posture power

DTR plantar abd.reflex cremastic Sensory

cerebellar autonomic(bladder,bowel,sweating,erectile dysfunction)

Gait walk with support walk without support armswing

UPDRS scoring Hoehn &yahr staging

(for all idiopathic parkinson's disease cases)

Olfactory function tests

1)Odour identification test score -	Mild	Moderate	Severe
2)Odour discrimination test	Normal		Impaired
3)Odour threshold test	Normal	Elevated	

Investigations

TC	DC	ESR	HB	Urea	Sugar	Creatinine	Lipid profile
Xray PNS(to ruleout sinusitis)							CT Brain
MRI Brain(in cases of PSP,MSA,Young onset parkinsonism)							

Treatment History

Drugs	Duration of treatment	Response to treatment
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MASTER CHART

SL No	S E X	A G E	Type Of Parkin.	Duration Of Illness (years)	Symptoms& signs	H&Y stage	UPDRS Score (Out of 176)	Past history	CT Brain	MRI	Olfact dysfn
1	M	52	I.P	2	Hypo,tr,Rigi u/l	1.5	42	HT	N	-	Moder
2	M	64	I.P	3	Hypo,tr,rigi b/l	3	73	HT/ DM	N	-	severe
3	F	59	I.P	2	Tr,rigi,u/l	1.5	54	-	N	-	moder
4	M	47	I.P	1	Hypo,tr,b/l	3	89	HT	N	-	moder
5	M	41	MSA	2	Hypo,rigi, Cerebellar b/l	3	98	-	-	T2 hyper In M.B, Pons	mild
6	M	55	I.P	4	Hypo,tr,rigi,b/ l	4	132	HT/ DM	N	-	severe
7	M	54	I.P	2	Hypo,tr,rigi,b/ l	3	112	-	N	-	severe
8	M	46	I.P	1	Hypo,tr,rigi,b/ l	2.5	61	HT	N	-	moder
9	F	53	I.P	3	Tr,rigi,hypo,b /l	4	145	HT	N	-	severe
10	M	67	I.P	4	Hypo,tr,rigi,b/ l	3	98	HT	N	-	Moder
11	M	62	I.P	3	Hypo,tr,rigi,b/ l	4	142	HT	N	-	severe
12	M	55	V.P	3	Hypo,rigi, u/l	2	56	HT	Infar In lt. B.Gan glia	-	normal
13	M	70	I.P	4	Hypo,tr,rigi,b/ l	4	141	-	N	-	severe
14	M	59	I.P	3	Hypo,tr,rigi,b/ l	3	95	-	N	-	moder
15	M	72	I.P	4	Hypo,tr,rigi,b/ l	3	101	HT	N	-	severe
16	M	67	I.P	2	Hpo,tr,rigb/ll	3	105	-	N	-	moder
17	F	53	V.P	3	Hypo,rigi, b/l	4	143	HT, DM	Rt gang.c ap.inf	-	normal
18	M	48	MSA	3	Hypo,rigi, b/l,cerebella auton.dysfn	3	111	-	-	thinnin g of br. stem	normal

19	F	56	I.P	2	Hypo,tr,rigi,b/ l	4	154	HT	N	-	severe
20	M	47	I.P	1	Hypo,tr,rigi,u/ l	2	59	-	N	-	moder
21	M	59	I.P	2	Hypo,tr,rigi,b/ l	3	87	-	N	-	severe
22	F	72	I.P	4	Tr,hypo,rigi,b/ l	4	143	HT	Mild Corti Atrop	-	severe
23	M	54	I.P	3	Hypo,tr,rigi,b/ l	3	125	HT	N	-	moder
24	M	73	I.P	4	Hypo,tr,rigi,b/ l	2.5	52	-	N	-	moder
25	M	48	I.P	3	Tr,hypo,rigiu/ l	2	58	-	N	-	moder
26	M	60	V.P	4	Hypo,rigi, b/l	3	89	HT/ DM	Lt lenti. infar	-	normal
27	M	64	I.P	3	Hypo,tr,rigi, b/l	3	96	-	N	-	severe
28	M	59	I.P	2	Tr,hypo,rigiu/ l	2	59	HT	N	-	moder
29	F	68	I.P	3	Hypo,tr,rigi b/l	4	145	HT	N	-	severe
30	M	74	I.P	4	Tr,hypo, Rigi,b/l	3	104	-	N	-	moder
31	M	24	SCA3	4	Rigi,hypo, Cere,pyr	3	75	-	Cerebe llar Atrop	-	normal
32	M	56	I.P	3	Hypo,tr,rigi b/l	3	97	HT	N	-	severe
33	M	48	PSP	3	V.gaz.palsy Hypo,rigi, ps.bulb.pals	4	96	-	-	Midbr atroph y	normal
34	M	57	I.P	2	Hypo,tr,rigi b/l	2.5	98	-	N	-	moder
35	F	51	I.P	4	Hypo,tr,rigi	3	132	DM	N	-	severe
36	M	59	I.P	1	Hypo,tr,rigi b/l	3	87	-	N	-	moder
37	M	37	F.P	2	Hypo,tr,rig,	3	85	F/H	N	-	moder
38	F	46	MSA	4	Hypo,rigi, Auton.dysfn	3	87	-	N	Thinn of pons	normal
39	M	63	I.P	2	Hypo,tr,rigi b/l	2.5	61	-	N	-	moder

40	M	48	V.P	4	Hypo,rigi u/l	2	32	DM	Infar in Rt puta	-	normal
41	F	54	I.P	2	Hypo,tr,rigi b/l	4	143	HT/D M	Lacuin far co.ra	-	severe
42	M	45	I.P	4	Tr,hypo,rigi b/l	3	97	HT	N	-	moder
43	M	55	MSA	3	Hypo,rigi Cereb,autond ysfn	4	134	-	N	thinnin g of br. stem	mild
44	M	47	I.P	2	Tr,hypo,rigi b/l	3	96	DM	N	-	moder
45	M	45	PSP	3	Ver.gaz.pals Hypo,rigi, Pse.bul.pals	3	102	-	N	thinnin g of mid brain	normal
46	M	67	I.P	4	Tr,hypo,rigi b/l	4	146	DM	N	-	severe
47	F	48	I.P	3	Hypo,tr,rigi b/l	3	112	HT	N	-	severe
48	M	27	SCA1	2	Hypo,rigi, Cerebellar signs	2.5	35	No fam.h/ o	Cerebe llar Atrop	-	normal
49	M	49	I.P	1	Tr,hypo,rigi u/l	2	32	-	N	-	moder
50	F	56	I.P	2	Hypo,tr,rigi b/l	3	62	-	N	-	moder
51	M	65	I.P	4	Tr,hypo,rigi b/l	4	148	HT	N	-	severe
52	M	64	V.P	3	Hypo,rigi u/l	3	70	HT/D M	Infar In Lt Cauda	-	normal
53	M	33	F.P	2	Hypo,rigi, b/l	3	69	Family h/o	N	-	mild
54	M	66	I.P	4	Tr,hypo,rigi b/l	4	145	-	N	-	severe
55	M	69	I.P	3	Hypo,tr,rigi b/l	3	98	-	N	-	severe
56	F	48	PSP	2	Ver.gaz.pals Hypo,rigi Ps.bul.pals	3	87	-	-	thinnin g of mid brain	normal
57	M	60	I.P	4	Hypo,tr,rigi b/l	2.5	40	-	N	-	moder
58	M	58	I.P	4	Tr,hypo,rigi	3	99	-	N	-	moder

					b/l						
59	F	70	I.P	3	Hypo,tr,rigi b/l	4	156	HT	N	-	severe
60	F	51	MSA	4	Hypo,rigi, Cerebellar Auton.dysfn	3	95	-	N	thinnin g of brain stem	normal
61	M	48	I.P	3	Tr,hypo,rigi b/l	2.5	61	HT	N	-	moder
62	F	67	V.P	2	Hypo,rigi b/l	3	65	HT/D M	Infar Inb/l basal gang	-	normal
63	F	56	I.P	4	Hypo,tr,rigi b/l	3	76	HT	N	-	moder
64	M	73	I.P	2	Tr,hypo,rigi b/l	4	123	HT	N	-	severe
65	M	54	I.P	1	Hypo,tr,rigi b/l	4	143	-	N	-	severe
66	F	55	I.P	3	Tr,hypo,rigi b/l	3	64	HT	N	-	moder
67	M	44	I.P	2	Hypo,tr,rigi b/l	2.5	43	-	N	-	moder
68	M	56	I.P	3	Hypo.tr,rigi	4	155	HT	N	-	severe
69	M	47	I.P	2	Tr,hypo,rigi b/l	3	63	-	N	-	moder
70	M	68	I.P	2	Hypo,tr,rigi b/l	3	65	DM	N	-	moder

H&Ystage-Hoehn&Yahr stage,UPDRS-Unified Parkinson's Disease Rating Scale,
hypo-hypokinesia,rigi-rigidity,tr-tremor,u/l-unilateral,b/l-bilateral

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